TRAMETINIB (Mekinist)

INDICATION (ICD10) C48, C56

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (TRAM1)

1. Trametinib monotherapy for low grade serous ovarian or peritoneal cancer which has recurred or progressed following at least one platinum-based chemotherapy regimen. Not previously received any MEK inhibitors. PS 0 or 1. (unlicensed)

REGIMEN

Days 1 to 28	**TRAMETINIB**	2mg	oral	once daily

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 28 days until disease progression. Formal medical review as to how trametinib is being tolerated and whether treatment with trametinib should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

ADMINISTRATION

Trametinib is available as 0.5mg and 2mg tablets.
Swallow both whole with water, at least 1 hour before or at least 2 hours after a meal.
Grapefruit and grapefruit juice should be avoided.

ANTI-EMETICS

Low emetic risk

CONCURRENT MEDICATION REQUIRED

Trametinib	None required

INVESTIGATIONS

Blood results required before SACT administration

FBC, U&E including Mg^{++}, LFTs and LDH Neutrophils x 10^9/L ≥1.0 provided patient is well Platelets ≥100x10^9/L	baseline and every cycle
Calculated creatinine clearance at the Consultant's discretion	baseline and every cycle
Serum creatinine	baseline and every cycle
Cardiac function (ECG/ECHO/MUGA)	As per network policy
Blood pressure	baseline and every cycle
CA125	baseline and day 1 every cycle or as required
Virology	before cycle 1 if not previously checked
Weight	baseline and every cycle

MAIN TOXICITES AND ADVERSE REACTIONS

Trametinib	Cutaneous squamous cell carcinoma New primary melanoma Non-cutaneous secondary / recurrent malignancy Haemorrhage Renal failure Pancreatitis LVEF reduction, Hypertension Pyrexia

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Trametinib	Effect of anticoagulants many be decreased. Antiviral exposure may be decreased. CYP3A4, CYP2C and CYP2B6 inducers should be avoided. Many interactions check carefully. Grapefruit and grapefruit juice should be avoided

DOSE MODIFICATIONS

Dose level	Trametinib dose
Full dose	2mg od
First reduction	1.5mg od
Second reduction	1mg od

Grade 1 or grade 2 (tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (intolerable) or grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce both by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until grade 0-1 and reduce both by one dose level when resuming therapy.

Pneumonitis / interstitial lung disease
Withhold trametinib in suspected pneumonitis or interstitial lung disease, and permanently discontinue if diagnosis confirmed. No dose reduction of dabrafenib is required.

Pyrexia
Patient's temperature is ≥38.5^{o}C dabrafenib should be interrupted. Evaluate for signs and symptoms of infection. Treatment may be restarted once the fever resolves with paracetamol or non-steroidal anti-inflammatory agents. If the fever is associated with other severe signs and symptoms (e.g. severe rigors, hypotension, acute renal insufficiency), dabrafenib should be restarted with a dose reduction, or alternate day dosing, once the fever resolves, as clinically appropriate. No dose reduction of trametinib is required.

Uveitis
No dose modifications are required for uveitis as long as effective local therapies can control ocular inflammation. If uveitis does not respond to local ocular therapy, dabrafenib should be withheld until resolution of ocular inflammation and then dabrafenib should be restarted reduced by one dose level. No dose modification of trametinib is required.

Retinal pigment epithelial detachment (RPED)

Grade 1 RPED	Continue treatment with retinal evaluation monthly until resolution. If RPED worsens follow instructions below and withhold trametinib for up to 3 weeks.
Grade 2-3 RPED	Withhold trametinib for up to 3 weeks
Grade 2-3 RPED that improves to grade 0-1 within 3 weeks	Resume trametinib at a lower dose (reduced by 0.5mg) or discontinue trametinib in patients taking trametinib 1mg daily.
Grade 2-3 RPED that does not improve to at least grade 1 within 3 weeks	Discontinue trametinib permanently.

Hepatic impairment
Trametinib
No dose adjustment for patients with mild or moderate renal impairment.
Use in caution with severe impairment.

Renal impairment
Trametinib
No dose adjustment for patients with mild hepatic impairment.
Use with caution in moderate or severe impairment.

REFERENCES
NHSE policy

Assessments

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Clinical assessment	X		Pre cycle		Pre cycle	Every cycle
SACT assessment (PS and toxicities)	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E, calcium & LFT, LDH	X	X	X	X	X	Every cycle
CA125	X	X	X	X	X	Every cycle as required
CrCl	X	X	X	X	X	Every cycle
Blood pressure	X	X	X	X	X	Every cycle
Cardiac function						Network policy
CT scan	X					At cycle 6, Inform consultant team if not booked
Informed consent	X					Verbal each cycle
Height	X					
Weight recorded	X	X	X	X	X	Every cycle